The effect of venous thrombus location and extent on the development of post-thrombotic signs and symptoms

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Objective: **This prospective study determined the incidence of signs and symptoms of chronic venous disease and recurrent venous thrombotic events (VTE) in relation to the location and extent of the initial venous thrombus.**
Methods: **A first episode of acute deep vein thrombosis (DVT) occurred in 120 lower extremities of 105 patients (59 men; mean age, 54 years [range, 23-82 years]). Patients who presented with pain, swelling, or signs and symptoms of pulmonary embolism of <10 days were included. The DVT was diagnosed with duplex ultrasound (DUS) imaging. Patients were grouped by those having thrombosis in one venous segment (group A) or multiple levels (group B). Patients were treated with heparin and warfarin. Patients with at least 1-year of follow-up with clinical and DUS were included.**
Results: **No difference was found in the duration of signs and symptoms at presentation. The median follow-up was 3.4 years (range, 1.2-7 years). More symptomatic limbs were seen in group B (71 of 79) compared with group A (21 of 41; $P < .001$). Post-thrombotic syndrome (PTS) was more advanced in group B vs group A, including the prevalence of skin damage and ulceration (61 of 79 vs 26 of 41, $P < .001$; 29 of 79 vs 6 of 41, $P = .019$, respectively). Limbs with calf DVT that had focal thrombosis were most often asymptomatic. Calf thrombosis in patients with proximal DVT produced the highest prevalence of PTS. Venous claudication was exclusively found in group B and was present only when iliac veins were involved. Recurrent thrombosis had a trend for a higher prevalence in group B (5 of 41 vs 16 of 79, $P = .39$). Reflux, obstruction, or a combination of the two were more common in group B (61 of 79) vs group A (15 of 41; $P < .0001$). Limbs with both reflux and obstruction were more likely to develop skin damage (group A, 5 of 6 vs 1 of 35, $P < .0001$; group B, 24 of 29 vs 5 of 50, $P < .0001$).**
Conclusions: **Recurrent thrombosis and skin damage is more likely to develop in patients with multiple sites of thrombosis than in those with thrombosis in a single vein segment. Patients with reflux and obstruction presented more skin damage than those with reflux or obstruction alone. Involvement of the calf veins in the presence of proximal vein thrombosis increased the likelihood for PTS. (J Vasc Surg 2008;48:407-12.)**

Acute venous thrombosis is a common problem and often leads to thrombus propagation, pulmonary embolism (PE), recurrent events, and post-thrombotic syndrome (PTS). The latter is frequent, occurring in 30% to 60% of patients that have venous thromboembolism (VTE).[1,2] This chronic condition includes telangiectasia, varicose veins, pigmentation, heaviness, swelling, venous claudication, and ulceration rarely leading to amputation.[3] The social and economic burden of PTS is considerable, with significant impact on quality of life.[4]

There remain conflicting results regarding the mechanism of PTS and whether proximal or distal deep vein thrombosis (DVT) is more likely to be associated with symptoms. Several studies have compared the extent and location of acute DVT with the presence and severity of PTS. However, these findings are given segmentally in different reports and some results are conflicting, making it difficult to extract solid conclusions. This prospective study was designed to determine the incidence of signs and symptoms of chronic venous disease (CVD) and recurrent VTE in relation to both the location and extent of the initial venous thrombus.

PATIENTS AND METHODS

Patients with a first episode of acute DVT in the lower extremity were included. These patients presented with pain, swelling, or signs and symptoms of PE of <10 days. Diagnosis of DVT was by duplex ultrasound (DUS) imaging. In some patients with inferior vena cava (IVC) and iliac thrombosis, diagnosis was by venography, either by computed tomography (CT) or magnetic resonance imaging, or phlebography, but these were confirmed by DUS. Patients were separated into two groups. Group A patients had isolated thrombosis in one venous segment (ie, in the popliteal vein only). Group B patients had at least two different levels involved (ie, the popliteal and femoral veins). Both groups were treated with heparin and warfarin.

Excluded from the study were patients with previous DVT, thrombolysis, signs and symptoms of CVD before thrombosis, a short life expectancy (<2 years), immobility (unable to walk), major bleeding requiring interruption of anticoagulation, and those with an ankle-brachial index

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(ABI) <0.8. Patients with CVD were excluded by clinical examination and DUS. All patients had to have at least 1 year of follow-up by clinical examination and DUS.

The signs and symptoms of CVD were recorded using the CEAP system.[5] Causes for thrombosis were recorded in detail. This included most of the well-known factors for VTE, such as trauma, surgery, catheterization, thrombophilia, family history, malignancy, and prolonged travel. Family history was positive when at least one first-degree relative had an episode of VTE during traveling when it was uninterrupted for >4 hours.

Symptoms of itching, burning sensation, pain, heaviness, and venous claudication were recorded. Venous claudication was considered to be present when patients were unable to walk more than a block without a pain despite having an ABI of >0.8. These patients had swelling and the limb was feeling tighter after walking.

Distribution and extent of reflux, obstruction, and recurrent DVT was assessed by DUS. Patients with signs and symptoms of PE underwent spiral CT. Recanalization was considered complete when no intraluminal material was detected, nearly complete when wall thickening or a few intraluminal webs were seen, partially complete when intraluminal material was detected, and absent when the whole lumen was occluded. Limbs were separated into normal, those having reflux, obstruction, and those with combined reflux and obstruction.

DUS was performed with multifrequency linear array transducers. Curvilinear array of 2- to 3-MHz was used in obese patients and for the iliocaval veins. Detection of DVT was performed in the supine position. IVC and iliac vein obstruction was tested in the supine and in the lateral decubitus position with the arm placed behind the head ipsilateral to the side of imaging. The infrainguinal veins were examined in the supine position. When the imaging was not adequate, such as the inability clearly delineate a duplicated femoral or popliteal vein, it was performed in the sitting or standing position. The reflux test was performed in the standing position. If the patient was unable to stand for long, the groin area was examined in the standing position and the rest of the examination was in the sitting position.

The cutoff value for reflux was set at 1 second in the common femoral, femoral, and popliteal veins; at 0.5 seconds in the deep femoral, deep calf veins, and superficial veins; and at 0.35 seconds in the perforator veins.[6] Manual compression was used in all areas in all venous segments. If this maneuver had a negative result in the proximal femoral and deep femoral veins and higher, the Valsalva maneuver was used as well. In limbs with significant edema, dorsi/plantar flexion was used when the result of manual compression was negative.

The criteria used for the diagnosis of acute and chronic thrombosis have been published elsewhere in detail.[7] The diagnosis of recurrent thrombosis was made by using the following criteria: extension of thrombus of >9 cm, noncompressibility of a vein segment that has been previously recanalized, and enlargement of the thrombus thickness by ≥2 mm.[8-10]

Table I. Causes of thrombosis

Cause	*Group A, No.*	*Group B, No.*
Family history[a]	3	6
Trauma	6	8
Surgery	8	11
Thrombophilia	4	17
Travel >4 hours	2	5
Extrinsic compression	2	4
Catheter	4	5
Tumor	2	3
Unknown	7	8
Total	38	67

[a]Family history was present in 5 additional patients in group A and in 7 in group B that had also one of the other factors present.

After the initial DUS at diagnosis, two clinical examinations and a repeat DUS were performed in the first 6 months, and a clinical examination and DUS were repeated at 1 year and then yearly thereafter. Because these patients had known thrombosis, DUS was done for both obstruction and reflux. Clinical examination and DUS were also done whenever the patients had new signs and symptoms of VTE.

Statistical analysis. Descriptive statistics were used to analyze patient characteristics. A two-tailed *t* test was used to analyze continuous data, and comparison of proportions was performed with a χ^2 test. The Fisher's exact test was used when the expected value in any of the cells was <5. Statistical significance was set at $P < .05$.

RESULTS

From an original 192 consecutive patients, the study included 120 limbs of 105 patients (59 men and 46 women) who were a mean age of 54 years (range, 23-82 years). Groups A and B were comparable in age and sex. Excluded were 45 patients owing to previous DVT (n = 8), CVD before DVT (n = 11), early fatal PE (n = 2), short life expectancy (n = 6), immobility (n = 3), major bleeding (n = 3), and thrombolysis treatment (n = 12). The remaining 42 patients were excluded because they did not complete at least 1 year of follow-up, either because they chose not to come (n = 36) or because they moved to another area (n = 6). The causes for thrombosis are reported in Table I. Thrombophilia alone or combined with cancer had a trend for a higher prevalence in group B (20 of 79) compared with group A (6 of 41; $P = .2$). At presentation, group A and group B had similar duration of signs (range, 1-9 days vs 1-7 day) and symptoms (range, 2-8 days vs 1-6 days). The median follow-up was 3.4 years (range, 1.2-7 years).

The distribution and extent of thrombosis as well as the prevalence of signs and symptoms are reported in Tables II and III. The extent of thrombosis was longer in group B because these patients had multisegmental thrombosis and also had more symptomatic limbs (21 of 41 vs 71 of 79, $P < .001$). This was true for all symptoms, whether examined together or separately.

Table II. Location of thrombi and signs and symptoms in patients with isolated vein thrombosis

Segment	*Patients, No.*	*Limbs, No.*	
		Signs	*Symptoms*
Inferior vena cava	3	4[a]	2
Common iliac vein	2	2	1
External Iliac vein	2	2	1
Common femoral vein	6	6	4
Femoral vein	3	1	1
Popliteal vein	7	6	5
Calf veins	15	7	7
Total	38	28	21

The total number of patients was 38 and the limbs 41.
[a]Patients with inferior vena cava thrombosis could have bilateral signs and symptoms.

Table III. Distribution and extent of thrombosis, signs, and symptoms in patients with multisegmental deep venous thrombosis

Segments	*Patients, No.*	*Limbs, No.*		
		No.	*Signs*	*Symptoms*
IF ± IVC	7	9	8	8
IF + fem-pop	9	10	8	9
IF + fem-pop + calf	11	13	13	13
Fem-pop	16	19	14	18
Fem-pop + calf	24	28	26	23
Total	67	79	69	71

Fem-pop, Femoral-popliteal; *IF*, iliofemoral; *Pop*, popliteal.

Table IV. CEAP classification in patients with isolated vein thrombosis

Segment	*Limbs, No.*				
	Total	*Class 0-1*	*Class 2-3*	*Class 4[a]*	*Class 5-6*
Inferior vena cava	6	2	3	1	0
Common iliac vein	2	0	2	0	0
External iliac vein	2	1	1	0	0
Common femoral vein	6	1	4	1	0
Femoral vein	3	2	1	0	0
Popliteal vein	7	1	4	2	0
Calf veins	15	8	5	2	0
Total	41	15	20	6	0

[a]Four limbs were in CEAP class 4A and 2 were in class 4B.

The CEAP classification for both groups in relation to the distribution of thrombosis is summarized in Tables IV and V. More advanced PTS was found in group B (61 of 79) vs group A (26 of 41; $P < .001$), including the prevalence of skin damage and ulceration (29 of 79 vs 6 of 41, $P = .019$). Limbs with calf DVT that had focal thrombosis or only one vein involved remained in CEAP class 0 and were most often asymptomatic, and those with thrombosis in multiple calf veins developed symptoms and were most often in CEAP class 3 and, occasionally, in class 4.

Table V. CEAP classification in patients with vein thrombosis in multiple segments

Segment	*Limbs, No.*				
	Total	*Class 0-1*	*Class 2-3*	*Class 4[a]*	*Class 5-6*
IF ± IVC	9	1	4	3	1
IF + fem-pop	10	2	4	3	1
IF + fem-pop + calf	13	0	6	5	2
Fem-pop	19	5	8	4	2
Fem-pop + calf	28	2	18	6	2
Total	79	10	40	21	8

Fem-pop, femoral-popliteal; *IF*, iliofemoral; *Pop*, popliteal.
[a]Thirteen limbs were in CEAP class 4A and 8 were in class 4B.

Venous claudication was exclusively found in group B (7 of 79) and was present only when iliac veins were involved.

Calf thrombosis in one vein segment resolved faster and produced no signs and symptoms of CVD. Patients with multiple calf vein involvement presented with swelling and, in two occasions, skin changes. The presence of calf vein thrombosis in patients with proximal DVT increased the likelihood they would present with post-thrombotic signs and symptoms (proximal veins, 30 of 38 vs proximal and calf veins, 39 of 41; $P = .04$). Only two of 28 patients with calf vein involvement in group B were in class 0 but were symptomatic, with itching and burning sensation in one and pain in the other; whereas in eight of 38 limbs with proximal DVT alone in class 0, four patients were symptomatic ($P = .17$).

Recurrent thrombosis had a trend for a higher prevalence ($P = .39$) in group B (16 of 79) compared with group A (5 of 41). The total number of recurrent thrombotic events was 20, because two patients had two recurrent episodes and another patient had three recurrent episodes. Clinical symptoms of PE were found in four patients (9.7%) in group A and in 16 (20.3%) of group B ($P = .2$). On spiral CT, PE was present in one of four in group A and in six of 16 in group B ($P = .6$ and $P = .2$ among all patients in both groups). Because of the study design, two additional patients with early fatal PE in group B were excluded from analysis. One fatal PE occurred at 42 months in group B.

Venous pathology was more common in group B (61 of 79) compared with group A (15 of 41; $P < .0001$). In group B, reflux was found in 23 limbs, obstruction in 6, and a combination of reflux and obstruction in 32; whereas in group A, reflux was found in 6, obstruction in 2, and a combination of reflux and obstruction in 6. Five of the six limbs with skin damage (CEAP classes 4 to 6) in group A had reflux and obstruction, and 24 of the 29 limbs with skin damage in group B had reflux and obstruction; therefore, limbs with both reflux and obstruction were more likely to develop skin damage in either group (group A, 5 of 6 vs 1 of 35, $P < .0001$; group B, 24 of 29 vs 5 of 50, $P < .0001$).

All eight limbs in which an ulcer developed had a multisegmental thrombosis (group B), of which four had a recurrent DVT and one was in a patient who was obese. All

but one of these patients were aged >55 years. One ulcer developed at 2 years, one at 3 years, and six at >3 years. Of the limbs that developed skin changes (6 in group A and 21 in group B), 2 appeared in the first year, 3 in the second year, 9 at 3 years, and 13 at >3 years.

DISCUSSION

The current study has a well-defined patient population in which the location and extent of thrombosis at baseline were established, coupled with a rigorous follow-up in which signs, symptoms, and severity of PTS, venous claudication, recurrent VTE, and clinically relevant PE were documented. The use of the CEAP classification system in a prospective fashion has allowed the study of the natural history of VTE in a consistent manner with a more valid comparison among the different groups.

The patients were selected to have a reasonable life expectancy such that enough time would elapse to document the frequency and severity of PTS. Patients with impaired mobility were excluded because this by itself would have been a significant risk factor for developing CVD. Patients with previous thrombosis, CVD, and an ABI <0.8 were also excluded to permit the study of the DVT impact on an unaffected extremity. The signs and symptoms of VTE were present for <10 days, allowing a uniform time effect of thrombosis in the involved extremity. Recurrent VTE was well documented and reported in relation to previous distribution of DVT.

Patients with symptomatic DVT are at an increased risk for recurrence.[11] It has been shown that PTS occurs in approximately 30% to 60% of patients 5 to 10 years after the initial DVT[1,2,12] and is approximately six times more likely to occur in patients with ipsilateral recurrent DVT.[1] In addition, Johnson et al[12] showed that abnormal findings in PTS patients are more common in the deep venous segments of the lower extremities compared with extremities without PTS.[12] In the current study, skin damage developed in 35 limbs (29%) at a mean follow-up of 3.4 years. The prevalence of skin damage was more common in group B, and the time taken for its development was >3 years in most limbs. Mild skin changes (CEAP class 4A) were noted in 15 limbs.

Effects of distribution and extent of thrombosis on PTS development in the IVC and iliac veins. With the exception of the calf veins, isolated thrombosis is uncommon.[13] In isolated thrombi, multiple pathways bypass the obstruction; therefore, the prevalence and severity of signs and symptoms in such patients was reduced compared with those with multisegmental thrombosis, even when the isolated thrombus was located in the IVC. Raju et al[13] found 10% of IVC obstructions had no, transient, or mild occlusive symptoms.[13] In a well-developed collateral system, IVC aplasia or hypoplasia is asymptomatic, whereas it is symptomatic if a well-developed system is not present.[13,14] Several collateral pathways bypass IVC obstruction, such as the azygous system, thoracolumbar, and thoracoepigastric veins. The azygous system may become so dilated that it appears as a left-sided IVC or duplicate venae cavae.[13,14]

Two-thirds of patients with iliocaval thrombosis had signs and symptoms ipsilateral to the iliac vein involved.[13] Given that the collateral network in IVC occlusion receives drainage from the iliac veins, it is crucial that the iliac veins remain patent. Patients with isolated iliac thrombosis in our study had mild signs and symptoms, but when the iliac vein was occluded in conjunction with other veins, the frequency and severity of PTS increased; for example, venous claudication occurred only in patients with multisegmental DVT where the iliac veins were involved.

Infrainguinal veins. Patients with isolated thrombosis below the iliac veins presented with mild signs and symptoms or were asymptomatic. Multiple collateral pathways are present at these levels.[15] The femoral vein is duplicated in 25% to 30% and the popliteal vein in 35% to 40% of the population, and triplications are seen in 3%.[16] In patients with isolated calf DVT, 60% were in CEAP class 0. These patients had focal thrombosis, and when multiple calf veins were thrombosed, the severity of PTS was worse.

Incompetence of the popliteal valves was more predictive of ulceration than recanalization or extent of DVT.[17] Poor popliteal vein function has been correlated with a worse clinical picture in the affected limb.[18] Johnson et al[19] found patients with popliteal vein abnormalities to be >3.5 times more likely to develop PTS. A high peak reflux velocity in the popliteal vein was a strong predictor for CVD,[20] whereas Meissner et al[21] showed the popliteal vein involvement to be among the major determinants of CVD. Accordingly, patients with multisegmental occlusion involving the popliteal vein are at a further risk for developing PTS.

It has been shown that in the presence of an occluded femoral vein, collateral pathways were rapidly established, with no evidence of collateral reflux.[22] Regardless of the nature of the collateral system involved, the extension of thrombosis seems to determine the severity of PTS. In our opinion this will more often occur in the presence of reflux or combined reflux and obstruction. It is unlikely to occur in patients with obstruction alone because it can be bypassed by the collateral veins, particularly in patients with duplicated veins.

In the current study, multisegmental DVT generated a measurable yet nonstatistically significant increase in incidence of venous claudication, recurrent DVT, and symptoms of PE compared with isolated DVT. A significantly increased prevalence of skin changes (CEAP C_4 classification) was noted compared with isolated DVT. These results are a function of the relatively small sample size.

Calf DVT. The current study found that thrombosis in multiple calf veins produced more frequent and more significant PTS than thrombosis in a single calf vein. To our knowledge, such an analysis has not been published, and this may partially explain the controversy on the development of PTS after calf DVT.[23] Recurrent ipsilateral episodes in patients with calf DVT have not been taken into account in previous studies. Calf vein involvement in the presence of proximal DVT was also found to increase the likelihood of PTS.[24] Yamaki et al[25] showed improved rates

of recanalization and thrombus resolution in calf vein thrombi compared with proximal vein thrombi, and this could explain why proximal DVT may be more significant in the development of PTS.[26,27] Calf thrombi may recanalize faster due to the effect of the calf muscle pump.[2] In addition, the thrombus load is related to the rate of recanalization.[28] The calf veins have less thrombus load than the proximal and therefore may recanalize faster.[29,30]

Recurrent DVT. Patients in group B had more often recurrent DVT and also a greater severity of symptoms. Ipsilateral recurrent DVT has an increased risk for developing PTS (hazard ratio, 6.4).[1] Ziegler et al[24] demonstrated that of the 30% of patients with recurrent DVT, recurrence was ipsilateral in 16%. Those with ipsilateral recurrent DVT developed PTS more often and also experienced more severe signs and symptoms.[24] They also showed that ipsilateral recurrence was a more important prognostic factor for developing PTS than was the initial extent of thrombosis.[24]

The segments initially involved are also important in the development of PTS. It has been shown that venous abnormalities present in the popliteal and tibial veins have a greater likelihood than proximal veins of leading to PTS.[12] The extent of segment involvement determines the severity of PTS. Initial multisegmental thrombi lead to a higher percentage of PTS development than single-segment thrombi.[12,19,24]

Effects of reflux and residual obstruction. Patients with residual thrombi are at an increased risk for obstruction and reflux secondary to recurrence or new thrombosis.[31,32] Recurrent thrombosis is more likely to occur in patients with previous iliofemoral thrombosis.[33] The presence of either reflux or obstruction has been shown to increase the risk for developing PTS. Limbs with PTS were 3.5 times more likely to have reflux and obstruction than limbs without.[19] Although obstruction in the absence of reflux is rare, the coexistence of reflux and obstruction is a common finding.[19] The current study found the combination of reflux and obstruction was more predictive of subsequent PTS than the presence of either condition alone, in accordance with the findings of multiple articles. This result corroborates the relationship suggested by Singh and Masuda.[34]

Limitations. Limitations of the study include presence of other factors that influence the development of CVD, such as obesity, age, and joint problems. Although a clinical examination was always performed, not all the patients had a repeat DUS study every year after the completion of the first year. The lack of physiologic testing did not permit us to study the effect of reflux, obstruction, and the calf muscle pump function. Asymptomatic patients with similar DVT distribution and extent were not tested to see if their natural history was comparable.

The small sample size in relation to various venous segments did not allow subdividing patients to analyze the anatomic variations in femoral and popliteal veins or to make statements for a single level in the proximal veins. This was also evident in cases with a low yield of symptoms, such as in patients with venous claudication.

The median follow-up was 3.4 years, but ideally, all patients should have completed a 5-year follow-up.

Not all the patients received the same treatment, because the use of unfractionated heparin and low-molecular-weight heparin was at the discretion of the treating physicians. The duration of the anticoagulation was not equal even if sometimes the location of thrombosis and the history of the patients were similar. All patients were asked to wear stockings for at least 2 years, but we did not monitor their use.

Some patients developed reflux in the superficial veins that were previously thrombosed, whereas others developed superficial vein reflux in the absence of thrombosis. The information on the extent of superficial vein thrombosis was not recorded in detail in more than a quarter of the patients and therefore the effect of the reflux in these veins was not accounted.

AUTHOR CONTRIBUTIONS

Conception and design: NL
Analysis and interpretation: NL, PP, TW, WS, SS
Data collection: NL, PP
Writing the article: NL, PP, TW, WS, SS
Critical revision of the article: NL, PP, TW, WS, SS
Final approval of the article: NL, PP, TW, WS, SS
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